Evaluation of risk factors for postoperative complications in rectal cancer patients

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ABSTRACT:
Introduction: The complications of surgical treatment for rectal cancer, particularly anastomotic leaks after anterior resection, are a significant clinical problem. We retrospectively analysed preoperative factors that may affect the occurrence of complications.

Material and Methods: A total of 392 rectal cancer patients were included in a retrospective analysis. A total of 257 anterior resections (AR) and 135 abdominoperineal resections (APR) were performed. The risk factors for early postoperative complications were analysed by logistic regression and receiver operating characteristic curves.

Results: The significant risk factors for severe complications (grade 3B and higher on the Clavien-Dindo scale) in the multivariate analysis were neutrophil to lymphocyte ratio > 5 (P = 0.047) in the AR group, age of the patients (P = 0.031) in the APR group, and coronary artery disease in both groups (P = 0.03, P = 0.011, respectively). There were no risk factors for anastomotic leaks in the AR group before the analysis was divided into early and late leaks. In the univariate analysis, the statistically significant risk factors for early leaks were preoperative neutrophil to lymphocyte ratio > 5 and peripheral blood platelet count, while late leaks were associated with coronary artery disease; however, in the multivariate analysis, these factors were not statistically significant.

Conclusions: The risk factors for severe postoperative complications were neutrophil to lymphocyte ratio > 5, advanced age of the patients and coronary artery disease. The different risk factors for early and late anastomotic leaks after anterior resection may indicate their different aetiologies.

KEYWORDS: anastomotic leak, anterior resection, postoperative complications, rectal cancer

ABBREVIATIONS

ACC – Age-Adjusted Charlson Comorbidity Index Score
AL – anastomotic leak
APR – although abdominoperineal resection
AR – anterior resection
AUC – area under the curve
BMI – body mass index
BSA – body surface area
CAD – coronary artery disease
CCIS – Charlson Comorbidity Index Score
CRP – C-reactive protein
ISREC – International Study Group of Rectal Cancer
NLR – neutrophil to lymphocyte ratio
PLR – platelet to lymphocyte ratio
PNI – Prognostic Nutritional Index
SIR – systemic inflammatory response

INTRODUCTION

Surgical treatment is still the most important part of the multimodality treatment of rectal cancer. In a selected group of patients, local tumour excision is possible; however, in most cases, radical resection with mesorectal excision is necessary. Although abdominoperineal resection (APR) still has its place in the treatment of rectal cancer, over the last several decades, the frequency of its performance has been reduced in favour of sphincter-preserving procedures. Although the techniques affect the same organ, anterior resection (AR) and APR differ in the characteristics of early postoperative complications, which is mainly determined by the presence of intestinal anastomosis in AR.

Anastomotic leak (AL) after AR is the most serious surgical complication of this procedure and occurs in 2–28% of cases; however, the frequency of its occurrence based on data in the literature is difficult to assess due to differences in the definition of leaks [1–5]. In addition, some reports indicate that AL is a negative prognostic factor for long-term outcomes in rectal cancer patients [6]. The factors for a predisposition to anastomotic leakage described in the literature vary depending on the authors and include a tumour location close to the anal verge, male sex, high body mass index (BMI), perioperative blood transfusion, long operation time, old age, lack of protective ileostomy, clinical stage IV disease, or preoperative radiotherapy [2, 4, 5, 7–11]. Based on these factors, attempts have been made to create prediction scales for leakage [12, 13].

Understanding the risk factors, especially those that are known before surgery, is useful in the development of operational tactics in individual patients, including the decision to perform a protective ileostomy or withdrawal from an anastomosis in favour of Hartmann’s procedure, which carries a lower risk of complications than anterior resection [14].
It cannot be ruled out that the risk factors for severe postoperative complications will vary between centres depending on the experience of the operating team, the number of treatments performed, the perioperative care or the characteristics of patients in a given area.

The aim of the study was to analyse postoperative complications and assess the known risk factors for their occurrence before surgery.

**METHODS**

Between May 2013 and November 2016 at the Oncological and Reconstructive Surgery Department, National Research Institute of Oncology in Gliwice Poland, a total of 257 (61.5%) AR, 135 (32.3%) APR and 26 (6.2%) Hartmann’s procedures were performed by open approach in patients diagnosed with rectal cancer. The 26 patients who underwent Hartmann’s procedure were excluded from further analysis due to the small size of the group. A total of 392 patients were subjected to a retrospective analysis (231 men and 161 women). All patients underwent planned operations by colorectal surgeons. The patients were aged 64.3 ± 9.6 (Me = 65) years, and the ages ranged from 29 to 85 years. The characteristics of the patients are presented in Tab. I. Body mass index (BMI) was calculated as [weight (kg)]/[height (m)]² and ranged from 14.0 kg/m² to 46.5 kg/m² (Me = 26.0 kg/m²). The body surface area (BSA) was calculated according to Mosteller’s formula 0.0167 x [weight (kg)]⁰.⁵ x [height (cm)]⁰.⁵ and ranged from 1.32 m² to 2.49 m² (Me = 1.85 m²) across the entire group. In 171 patients, preoperative radiotherapy was performed, and in 128 patients, preoperative chemoradiotherapy was performed. A total of 93 patients were not subjected to preoperative treatment. In most patients who underwent preoperative treatment, the period from the end of irradiation to surgery was at least 6 weeks. Preoperatively, we used oral mechanical bowel preparation and oral and intravenous antibiotic prophylaxis as a standard method. We did not use prolonged antibiotic prophylaxis. In all cases with complications, we used targeted antibiotic therapy based on culture and sensitivity testing. Rectal resections were performed using the total mesorectal excision technique. Colorectal anastomosis after AR was performed using the end-to-end stapler method. In the group of patients who underwent AR, protective loop ileostomy was performed in 56 (22%) cases.

The AR group and the APR were analysed separately due to the different characteristics of complications in these groups. The severity of the complications was assessed according to the Clavien-Dindo classification, and the complications were distinguished between infectious complications and severe complications (stage 3B and higher); in the group of patients who underwent anterior resection, additional ALs were also assessed.

AL, according to the International Study Group of Rectal Cancer (ISREC), was defined as a defect in the intestinal wall of integrity at the colorectal or coloanal anastomotic site, which leads to communication between the intra- and extraluminal compartments as well as pelvic abscesses in the proximity of the anastomosis [15, 16].

AL was diagnosed on the basis of clinical symptoms, rectum examination and/or radiological examination results (computed tomography with contrast given per rectum). Among the ALs, early leaks (up to 30 days from surgery) and late leaks (over 30 days from surgery) were distinguished from each other.

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>ANTERIOR RESECTION</th>
<th>ABDOMINO/PERINEAL RESECTION</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ± SD</td>
<td>63.5 ± 9.8</td>
<td>65.8 ± 9.0</td>
<td>0.028</td>
</tr>
<tr>
<td>Sex</td>
<td>M = 148(58%), F = 109(42%)</td>
<td>M = 83(61%), F = 52(39%)</td>
<td>0.5244</td>
</tr>
<tr>
<td>BMI ± SD</td>
<td>26.3 ± 4.1</td>
<td>26.4 ± 5.1</td>
<td>0.755</td>
</tr>
<tr>
<td>BSA ± SD</td>
<td>1.85 ± 0.20</td>
<td>1.84 ± 0.21</td>
<td>0.789</td>
</tr>
<tr>
<td>CCIS = 0</td>
<td>112(44%)</td>
<td>50(37%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>CCIS = 1</td>
<td>85(33%)</td>
<td>50(37%)</td>
<td>0.4003</td>
</tr>
<tr>
<td>CCIS &gt;= 2</td>
<td>57(22%)</td>
<td>35(26%)</td>
<td>0.4384</td>
</tr>
<tr>
<td>CAD</td>
<td>21(8%)</td>
<td>15(11%)</td>
<td>0.4535</td>
</tr>
<tr>
<td>Neoadjuvant RT</td>
<td>99(39%)</td>
<td>72(33%)</td>
<td>0.0069</td>
</tr>
<tr>
<td>Neoadjuvant RCT</td>
<td>80(31%)</td>
<td>48(36%)</td>
<td>0.4384</td>
</tr>
<tr>
<td>Stage IV disease</td>
<td>177(70%)</td>
<td>61(4%)</td>
<td>0.0027</td>
</tr>
<tr>
<td>Distance from anal verge:  1–5 cm</td>
<td>58(23%)</td>
<td>120(90%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6–10 cm</td>
<td>92(36%)</td>
<td>11(8%)</td>
<td></td>
</tr>
<tr>
<td>11–15 cm</td>
<td>105(41%)</td>
<td>3(2%)</td>
<td></td>
</tr>
</tbody>
</table>

BSA – body surface area, BMI – body mass index, CCIS – Charlson Comorbidity Index Score, CAD – coronary artery disease, NLR – neutrophil to lymphocyte ratio, RT – radiotherapy, RCT – radiochemotherapy

All bacterial or fungal infections were not related to AL; for example, abdominal or perineal wound infections, urinary tract infections, pneumonia, intraoperative abscess, etc., were qualified as infectious complications.

Among the risk factors for complications, age, sex, BMI, BSA, general condition according to the Zubrod scale, tumour distance from the anal verge, presence of distant metastases, comorbidities [both separately and according to the Charlson Comorbidity Index Score (CCIS) and Age-Adjusted Charlson (AAC) Comorbidity Index Scores] [17] and Prognostic Nutritional Index (PNI) were analysed. PNI was calculated as [albumin concentration (g/L) + 5 × [lymphocyte count (10³/µL)]]. Furthermore, the following preoperative peripheral blood parameters were assessed: white blood cell, neutrophil, lymphocyte, erythrocyte and platelet counts, erythrocyte sedimentation rate (ESR), and haemoglobin, as well as fibrinogen, C-reactive protein (CRP), albumin, total protein, CEA and CA 19-9 concentrations, neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR). Blood samples were taken 7–14 days before the operation.

In the statistical analysis, logistic regression was used to assess the impact of risk factors on the occurrence of the studied clinical events. The strength of the association between the analysed variables and the clinical event was classically expressed as an odds ratio (OR).
RESULTS

There were 2 (0.8%) deaths in the postoperative period after AR. In one case, the postoperative course was complicated by an early AL, and in the second case, by eversion. We did not find deaths after APR. In the entire group of patients, postoperative complications occurred in 106 (27%) cases, while complications that were grade 3B or higher according to the Clavien’s classification occurred in 42 (10.7%) cases. In the AR and APR groups, severe complications occurred in 34 (13.2%) and 8 (5.9%) patients, respectively (P = 0.0404).

ALs after anterior resection occurred in 29 (11.3%) cases in the entire group of 257 patients, including 18 early and 11 late leaks. There were no asymptomatic leaks (Grade A according to ISREC). The average time of onset of early leak symptoms was 7 days after surgery (from 4 to 14 days), while late leak symptoms occurred 56 days after surgery (from 32 to 90 days). Apart from one patient (Grade B according to ISREC), all patients required reoperation (Grade C according to ISREC), out of which, protective loop ileostomy was performed in 4 cases, drainage of the pelvic abscess was performed in one case (after prior loop ileostomy), and liquidation of the anastomosis was necessary in one case, and drainage of the pelvic abscess was sufficient in the second case.

We found slightly different risk factors for severe complications in both groups. In the univariate analysis, the significant risk factors for serious complications were coronary artery disease (CAD) (P = 0.008), NLR > 5 (P = 0.038) and CCIS (P = 0.033) in the AR group and CAD (P = 0.002) and age (P = 0.012) in the APR patients. In the multivariate analysis, a common factor for the AR and APR groups was coexisting CAD, P = 0.03 and P = 0.011, respectively. In addition, for the AR group, an important factor was NLR > 5 (P = 0.047), and for the APR group, the age of patients (P = 0.031). A ROC analysis for age in the APR group is shown in Fig. 1.

Analysing the group of patients after AR, we found that there were no statistically significant risk factors for ALs before the division into early and late leaks. In the case of early ALs, statistically significant risk factors in the univariate logistic analysis were NLR > 5 and the platelet count. In multivariate analysis, these factors did not achieve statistical significance (P = 0.13 and 0.071, respectively). The ROC analysis for platelets showed that for cut-off point = 268.5 (x103/µL), the sensitivity and specificity in the early AL prediction were 61.1% and 71.1%, respectively (Fig. 2.). In the case of late ALs, the only relevant risk factor in the univariate analysis was CAD. In the statistical analysis, there was no significant effect from loop ileostomy on the frequency of AL (P = 0.135).

When considering infectious complications, in the AR group, the significant factors in the univariate analysis were ESR, albumin concentration, PNI and the presence of a protective ileostomy. The multivariate analysis in this group showed that the only significant risk factor was a protective ileostomy (P = 0.036). The only significant risk factor in the APR group in the univariate analysis was ESR.

Statistically significant factors in the logistic regression are presented in Tab. II. There was no influence of the remaining examined factors on the risk of postoperative complications.
DISCUSSION

Patients who underwent AR or APR were subjected to separate analysis due to the different characteristics of complications in both groups. We have demonstrated that CAD is an important risk factor for severe postoperative complications. In our opinion, this factor should be treated as an equivalent to advanced atherosclerosis affecting the impaired blood supply to the anastomosis. Based on the available data, however, we were not able to retrospectively assess the severity of atherosclerosis in the study group in a different manner to confirm this hypothesis. Other factors significant in the multivariate analysis differed between both analysed groups. In the AR group, the additional factor was NLR > 5, indicating a significant effect of increased systemic inflammatory response (SIR) on the occurrence of serious complications in this group of patients. In contrast, the age of the patients, which was described in the literature as a risk factor, was important only in the APR group in our analysis; however, it should be mentioned that the average age in the APR group was higher than in the AR group [18]. The ROC analysis showed high sensitivity of this parameter in the prediction of severe complications in this group.

In the AR group, the majority of complications classified as grade 3B and above were ALs. In this group, the existence of different factors that correlated with early and late ALs indicates their different aetiologies, which is also reflected in their different clinical courses. Even though the risk factors for leakage did not achieve statistical significance in the multivariate analysis, we believe that they reflect a certain trend. Risk factors such as elevated NLR and platelet count in early leaks suggest a component of excessive SIR. This finding is in line with the observation of Miyakita et al. [9]. Preoperative NLR as a predictor of serious complications after colorectal surgery was also described by Josse et al. with a trend towards the prediction of AL [19]. Initially, NLR was described as a parameter for the assessment of SIR in critically ill patients by Zahorec [20]. Then, the evaluation of NLR by oncologists showed that NLR was an important prognostic factor in many cancers, confirming the negative prognostic value of an excessive inflammatory response [21–24]. We also found a correlation between the number of peripheral blood platelets and the occurrence of early ALs; however, the ROC analysis showed low sensitivity of this parameter in the prediction of early ALs. It is known that tumour cells stimulate the thrombogenesis process and that the number of peripheral blood platelets is a known prognostic factor in many cancers. The platelets, apart from their haemostatic function, influence the formation and persistence of the inflammatory process through the release of numerous biologically active substances. The participation of platelets in the process of tumour angiogenesis...

![Table II. Univariate and multivariate logistic regressions.](image-url)
and metastasis has also been described [25]. To the best of our knowledge, the relationship between the number of platelets and early leaks has not been demonstrated. We address another situation in the case of late ALs, which are never eliminated, may reach up to 25% [34]. In our material, where the only risk factor was CAD, the factor of insufficient blood supply to the anastomosis associated with peripheral atherosclerosis played an important role. Although the relationship between peripheral vascular disease and the risk of ALs has been described in the literature, to the best of our knowledge, it has not been shown to be typical for late ALs [2, 28]. In the literature, among the predisposing factors for the occurrence of late ALs, preoperative radio/chemotherapy emerged as a factor, which our analysis does not confirm [29, 30, 31]. We believe that the above factors (NLR, platelet count, and CAD) should be taken into account when deciding whether to perform a loop ileostomy.

Up to now, in our centre, the decision to perform a protective ileostomy has subjectively been made by the operator during surgery, with the main considerations being technical problems in the creation of the anastomosis and the distance of the anastomosis from the anal verge, where the so-called low anastomosis was predisposed to create the stoma. While the first factor was fully justified, our analysis shows that the height of the anastomosis is not significant.

In our material, we have not found the influence of loop ileostomy on the reduction in the frequency of symptomatic ALs; however, taking into account the above conditions of the decision for its creation, the inference is uncertain. Data in the literature indicate that the formation of a loop protective ileostomy may reduce the type of leak rate [7, 8, 32, 33]. It should be noted that the percentage of ileostomies, which are never eliminated, may reach up to 25% [34], and in elderly patients, the failure to close the stoma may reach up to 50% [35]. Moreover, the use of ileostomy is associated with additional possible complications. In our material, loop ileostomy was the only risk factor in the multivariate analysis for the occurrence of infectious complications in the group of patients after AR, who mainly experienced surgical wound infections. Bearing in mind the above considerations, the decision to perform a loop ileostomy should be made in justified cases. Preoperative radio- and chemoradiation do not affect the risk for anastomotic leaks in our material, which is also confirmed by reports from other centres [4, 36, 37]. It seems that the length of the period from the end of radiotherapy to surgery [5] plays a significant role in this case.

We also have not confirmed the impact on the risk of complications of several factors described in the literature, such as male sex, distance of the tumour from the anal verge, BMI or disseminated disease [8, 10, 38].

**CONCLUSIONS**

A common risk factor for severe complications in AR and APR was CAD. In addition, in both groups, we found different significant risk factors for their occurrence, including NLR > 5 and the advanced age of patients, respectively.

In the group of patients after anterior resection, after dividing the ALs into early and late leaks, we found different factors that correlated with the occurrence of leaks in both groups, which indicates different aetiologies. Even though they did not achieve statistical significance in the multivariate analysis, SIR factors and atherosclerosis have an influence trend on early leaks and late leaks, respectively. We believe that parameters of SIR with high values, such as NLR or peripheral platelet count and atherosclerosis, could be one of the predisposing factors for the formation of a loop ileostomy.

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**REFERENCES**


Competing interests: The authors declare that they have no competing interests.

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